

REMARKS

Entry of this Amendment is proper under 37 C.F.R. § 1.116, because the Amendment places the application in condition for allowance for the reasons discussed herein; does not raise any new issue requiring further search and/or consideration, because the amendments amplify issues previously discussed throughout prosecution; relates to matters of form rather than substance, because the added language was already present in the claims and thus presents no additional search burden; no new claims are added; and places the application in better form for an appeal should an appeal be necessary. The Amendment is necessary and was not earlier presented because it is made in response to arguments raised in the final rejection. Entry of the Amendment, reexamination, and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.116, are thus respectfully requested.

1. Status of the Claims

Claims pending: 1-14

Claims rejected: 1-3 and 7-9

Claims objected: 4-6 and 10-14

Claims allowed: None

Applicants amend claims 1 and 10 to more precisely recite the claimed subject. Support for the amendment can be found at least in the original claims. For example, the amendment of claim 10 can be found at least in original claim 11 and the Specification, lines 1-7, page 14. Applicants do not believe that the amendments add prohibited subject matter that is unsupported by the Specification as filed.

Cancellation of and amendments to the claims have been made without prejudice to or disclaimer of the subject matter contained therein. Applicants reserve the right to file a continuation and/or divisional on any subject matter canceled by way of amendment.

2. Acknowledgement of Priority

Applicants appreciate the Office's acknowledgment that all certified copies of the priority documents have been received.

3. Withdrawn Rejection

Applicants appreciate that the Office withdraws (1) the rejection of claims 4-6 and 10-14 under 35 U.S.C. § 103(a) over **WO 03/000698** (“the ‘698 publication”); and (2) the obviousness-type double patenting rejection over claims 6-7, 10, 12, and 14-15 of **U.S. Patent No. 7,247,652** (“the ‘652 patent”).

4. Rejection of claims 1-3 and 7-9 under 35 U.S.C. §103(a).

The Office maintains the rejection of claims 1-3 and 7-9 over the ‘698 publication.

4.1 Claims 1-2 and 7-8

The Office alleges that “Applicants’ claims teach known compounds with the addition of a radiolabel.” Office Action, page 3. The ‘698 publication allegedly discloses a valid reason or suggestion to modify the compounds. *Id.* The Office further alleges that claimed “straight or branched lower aliphatic alkoxy group” includes the methoxy group as shown in the ligand of Scheme 2 of the ‘698 publication. *Id.*, at 3-4.

Applicants traverse the rejection to the extent it applies to the amended claims. Structural similarity between compounds is not by itself sufficient to establish obviousness, *unless* “the prior art gives reason or motivation to make the claimed compositions.” *See In re Dillon*, 919 F.2d 688, 692, 16 U.S.P.Q.2d 1897, 1901 (en banc) (Fed. Cir. 1990); *Takeda Chem. Indus. Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 1356, 83 U.S.P.Q.2d 1169, 1174 (Fed. Cir. 2007).

The Office’s rejection is unsupported for at least the following reasons. First, Scheme 2 of the ‘698 publication teaches preparing radio-labeled methoxy-substituent. Claim 1 as amended no longer recites a radio-labeled methoxy-substituent. Instead, claim 1 now recites, *inter alia*, the following radio-labeled substituents:

- 1) a straight or branched lower aliphatic alkyl group;
- 2) a hydroxyl group;
- 3) an amino group;
- 4) a straight or branched lower aliphatic acylamido group;

5) a halogen atom; and

6) a straight or branched lower aliphatic haloalkyl group.

A methoxy group does not fall into any recited group. Furthermore, neither the '698 publication nor the Office provides any "reason or motivation" to make the claimed radiolabeled substitute. Accordingly, the alleged structural similarity is not by itself sufficient to establish obviousness. *See Dillon*, 919 F.2d at 692, 16 U.S.P.Q.2d at 1901; *Takeda*, 492 F.3d at 1356, 83 U.S.P.Q.2d at 1174.

Second, the radiolabeled substituent of the claimed compounds are exclusively at the 4-position (para-position) of the benzoyl group, while the *non-radiolabeled* substituents of the compounds disclosed in the '698 publication are at all three positions (ortho-, meta- and para-positions). *See* Office Action mailed November 24, 2009, pages 3-6. There is no suggestion to add a radiolabeled group to the 4-position in particular, over any other position, let alone an expectation that such a modification would have had an expectation of success. The Office is directed to the paragraph bridging pages 9-10 of the Specification:

TBOA occurs as four stereoisomers and the (2S,3S) compound shows the strongest activity among them. The substituent on the benzoyl ring may be located at three positions, i.e., ortho-, meta- and para-positions. *Studies on the structure-activity-relationship of these compounds clarified that the para-compound shows the strongest activity.* Therefore, in the following synthesis scheme the introduction of a radioactive substituent is shown by taking compounds having a (2S,3S)-configuration in the aspartic acid and having the substituent at the para-position on the benzoyl, though all isomers having different substitution or configuration manners are included in the scope of the present invention.

(emphasis added). There was no indication, absent testing, that substitution at one position over another would have produced a better activity. The finding is unexpected.

In fact, the '698 publication describes that strongest activity results from the *meta-position* of the amino group on the benzene ring, *not* the para-position. *See* page 8, lines 7-17 of the '698 publication. A skilled artisan, in view of the '698 publication would not have been directed to even try to modify the para-position. The Office also fails to provide any evidence showing there is guidance in the art to make and/or use the claimed compounds.

Finally, the presently claimed compounds and methods offer unexpected advantages. Scheme 2 of the '698 publication teaches preparing radio-labeled methoxy-substituent. The present application describes labeling, for example, with radioactive iodine (*e.g.*, claim 2 recites labeling with ^{125}I). The labeling with radioactive iodine offers at least the following advantages:

- 1) ^{125}I emits a gamma ray, which enables direct detection with brain imaging;
- 2) ^{123}I can be detected noninvasively in SPECT (single photon emission computed tomography) because of its shorter half-life; and
- 3) the binding activity of iodide-substitute ($\text{IC}_{50} = 4.8 \text{ nM}$) is higher than the methoxy-substituent ($\text{IC}_{50} = 12 \text{ nM}$).¹

Additionally, the present claims recite, *inter alia*, labeling with tritium gas (*e.g.*, claims 2, 10 and 13-14). The tritium gas labeling process is capable of producing purer products with a higher yield, compared to the methylation of a phenolic hydroxyl group as shown in Scheme 2 of the '698 publication. *See* right column under "Material and Methods," page 295, Shimamoto et al., 71 MOL. PHARMACOL. 294 (2007) ("Shimamoto") (enclosed as Exhibit II in the Amendment / Response filed May 24, 2010). The tritium-containing ethyl-substitute has the highest binding activity ($\text{IC}_{50} = 3.2 \text{ nM}$). *See* Specification, Table 2, page 25. Further, tritium gas labeling enables the development of a "binding assay," which is superior to the conventional "uptake assay." *See* Shimamoto, "Discussion" on pages 299-301.

In view of at least these arguments, amended claim 1 is nonobvious over cited references. Dependent claims 2 and 7-8 are likewise nonobvious for at least the same reasons. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

4.2 Claim 9

The Office alleges that claim 9 is obvious, because "the '698 publication teaches that its radiolabeled ligands are useful for identification of transporter proteins which, as demonstrated throughout the publication, include glutamate transporter proteins." Office Action, page 6.

¹ *See* Specification, Table 2, page 25; the '698 publication, Table 1, page 37. The IC_{50} was determined as the ability to inhibit the uptake of [^{14}C]-glutamic acid by human EAAT2 and EAAT3 stably expressed in MDCK (Madin-Darby canine kidney) cells or transiently expressed in COS-1 cells. *See* Specification, paragraph bridging pages 24-25.

Applicants traverse. Claim 9 depends indirectly from claim 1. Claim 1 as amended is nonobvious for at least the reasons discussed in Section 4.1 *supra*. Therefore, claim 9 is similarly nonobvious. Additionally, there is no teaching that would have led a skilled artisan to have identified and used the claimed compounds to identify or characterize glutamate transporter proteins.

Given at least these arguments, claim 9 is nonobvious over cited reference. Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of claim 9.

4.3 Claim 3

The Office alleges that the Y group recited in Claim 3 can be an organometallic group, which allegedly includes the *tert*-butyldimethylsilyl (TBS) group disclosed at Scheme 2 of the '698 publication. Office Action, page 6.

Applicants traverse. "[O]bviousness requires a suggestion of *all* limitations in a claim." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342, 68 U.S.P.Q.2d 1940, 1947 (Fed. Cir. 2003) (emphasis added). The Office must also establish that one of ordinary skill in the art would have had a reasonable expectation of success to practice the claimed invention. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991).

The Office's rejection is unsupported, because the Office mischaracterizes the term "organometallic group." The term "organometallic group" refers to a chemical group containing bonds between a carbon atom and a metal atom. *See, e.g.*, "Organometallic Chemistry" available at http://en.wikipedia.org/wiki/Organometallic_chemistry ("Organometallic chemistry is the study of chemical compounds containing bonds between carbon and a metal."). The *tert*-butyldimethylsilyl (TBS) group, however, is a commonly used protecting group containing a silicon atom. *See, e.g.*, "Silyl ether" available at http://en.wikipedia.org/wiki/Silyl_ether. The silicon atom is *not* a metal atom. Thus, the recited organometallic group differs from the TBS group disclosed in the '698 publication. There is no evidence on the record that the '698 publication teaches all elements of claim 3. Without all claim elements taught, there can be no expectation of success that the a skilled artisan would have made or used the claimed product predictably.

Given at least these arguments, claim 3 is nonobvious over the cited reference. Applicants respectfully request withdrawal of the rejection and allowance of claim 3.

5. Claims Objection

The Office objects to claims 4-6 and 10-14 as allegedly depending from a rejected base claim. Office Action, page 7. As discussed in Section 4 above, amended claim 1—the base claim—is nonobvious over cited reference. Accordingly, Applicants respectfully request withdrawal of the objection and allowance of the claims.

CONCLUSION

In view of the above arguments and amendments to the claims, Applicants submit that the claims are in condition for allowance and respectfully request reconsideration and timely allowance of the claims.

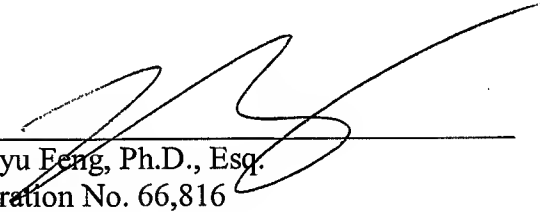
Should the Office have any questions or comments regarding Applicants' amendments or response, please contact Applicants' undersigned representative at (202) 230-5119. Furthermore, please direct all correspondence to the below-listed address.

In the event that the Office believes that there are fees outstanding in the above-referenced matter and for purposes of maintaining pendency of the application, the Office is authorized to charge the outstanding fees to Deposit Account No. 50-0573. The Office is likewise authorized to credit any overpayment to the same Deposit Account Number. If an Appeal fee is required to maintain pendency of the present application, the Office is authorized to charge the Appeal fee to the deposit account above and use this paper as a constructive Notice of Appeal.

Respectfully Submitted,

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By: _____


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